

## REMARKS

Claims 1, 4, and 7-24 are pending.

The Examiner has unequivocally stated that the Applicants' invention defined by the pending claims is anticipated by the Lambert '373 disclosure fundamentally because commercially available TPGS, for example, inherently contains 1.5% free tocopherol as an unavoidable impurity. The Examiner's articulated reasoning is that since the Applicants' invention defined by the claims necessarily, due to an inherent impurity, comprise free tocopherol the claims read-on the compositions taught by Lambert. The Applicants respectfully point out, however, that formulations contemplated by Lambert, *et al.*, in U.S. Patent No.6,458,373 all require calculated and intentional addition *free* tocopherol as a substantial and critical element of the formulation *per se*, for the express purpose of solubilizing drug compounds, in addition to any tocopherol otherwise unavoidably present. Indeed  $\alpha$ -tocopherol is indeed the touted beneficial ingredient for all compositions contemplated within the disclosure of Lambert, *et al.*, '373, i.e., "[t]he compositions of this invention contain  $\alpha$ -tocopherol as a carrier for therapeutic drugs"). See, e.g., '373 Col. 9, lines 14-15; Col. 21, line 49. Example 23 (the only etoposide example) includes, for example, **300mg  $\alpha$ -tocopherol** per 5ml.

However, in contrast to the teachings of Lambert, *et al.*, '373 *free*  $\alpha$ -tocopherol, *per se*, is detrimental to properties and efficacy of podophyllotoxin compositions as unequivocally shown in the evidence and side by side comparisons presented in the prosecution of instant application. The Examiner is respectfully referred to the rule 132 Declaration presented June 2, 2003 in this application as well as the second rule 132 Declaration executed by Dr. Valery Alakhov presented March 30, 2004. The addition of alpha-tocopherol (*free* tocopherol) in the amounts taught by Lambert, *et al.* to formulations comprising Etoposide and TPGS unequivocally dramatically reduces the solubility of Etoposide and leads to phase separation unless special emulsification procedure is used as

described in the Lambert, *et al.*, patent. Compositions of the present invention indeed eliminate the addition of tocopherol and thereby *minimize* the content of free  $\alpha$ -tocopherol as a detrimental factor of the formulation. In view of the Examiner's indication that commercially available TPGS inherently contains about 1.5% free tocopherol the Applicants now present a corollary amendment to the claims wherein not more than about 1.5% of said tocopherol is free tocopherol.<sup>1</sup>

The Applicants respectfully highlight to the Examiner that compositions of the present invention cannot be anticipated as a matter of law in view of the disclosure of Lambert, *et al.*, '373, e.g., Example 23; this example does not provide a description of drug formulation, but provides a content of  $\alpha$ -tocopherol in TPGS as in a raw material. All compositions contemplated by Lambert that contain a pharmaceutical agent (particularly a podophilotxin) require the addition of *free*  $\alpha$ -tocopherol, *per se*. The Applicants respectfully request the Examiner to withdraw the rejection.

The Applicants further respectfully highlight to the Examiner that compositions of the present invention cannot be obvious as a matter of law in view of the disclosure of Lambert, *et al.*, '373 because a paramount factor, i.e., the active ingredient, expressly required by Lambert, namely  $\alpha$ -tocopherol, *per se*, is reduced to a minimum practical amount in the Applicants' compositions resulting in improved pharmacological properties, in fact, due to increased aqueous solubility of drug compounds. The Applicants respectfully request the Examiner to withdraw the rejection.

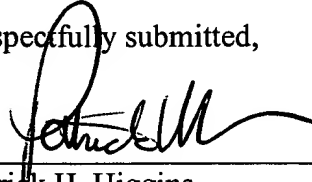
For all the foregoing reasons, the Applicants submit that Claims 1, 4, and 7-24 are in condition for allowance.

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<sup>1</sup> The Applicants moreover point out that Lambert Example 26 is not representative of drug formulations exemplified within the disclosure. Example 26 is merely a representation of *a component of* contemplated formulations. All formulations contemplated by Lambert, however, necessarily include *added* tocopherol, *per se*, in addition to any inherent tocopherol that must otherwise be present.

The Commissioner is authorized to treat this response requiring a petition for an extension of time under 37 CFR 1.136 for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. The Commissioner is authorized to charge any deficiency or credit any overpayment in connection herewith to Deposit Account No. 13-2165.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Patrick H. Higgins", written over a horizontal line.

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